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FILING DATE: ***January 15, 2004***

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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Additional inventors are being named on the 2ND *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PHOSPHOSPHINGOLIPIDS, METHODS FOR THEIR PREPARATION AND DIFFERENT USES THEREOF

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[Page 1 of 2]

Respectfully submitted,

SIGNATURE [signature]

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Date January 15, 2004

REGISTRATION NO. 41,827
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Docket Number 25932

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[Page 2 of 2]

Number 2 of 2

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PHOSPHOSPHINGOLIPIDS, METHODS FOR THEIR PREPARATION AND DIFFERENT USES THEREOF

FIELD OF THE INVENTION

This invention relates to phosphosphingolipids, methods for their preparation and different uses thereof.

BACKGROUND OF THE INVENTION

In recent years, phosphosphingolipids such as sphingomyelins (SPMs) are gaining interest for pharmaceutical and therapeutic applications.

Sphingolipids and especially SPMs are unique in their chemical stability. Lacking ester bonds and polyunsaturated acyl chains they resist hydrolysis and oxidation during storage and formulation processing. Therefore, SPMs are excellent candidates for drug delivery formulations based on liposomes and other lipid assemblies. Having full control over the composition one can design SPMs which, when present in a lipid bilayer under physiological conditions (e.g. at body temperature) may be in a fluid (i.e., *N*-oleoyl sphingomyelin), or solid (i.e., *N*-stearoyl sphingomyelin) state, or design SPMs which enable the generation of thermo-sensitive liposomes.

Another unique feature of SPMs is their high affinity for cholesterol thereby serving as potential drug to induce reverse cholesterol transport in cardiovascular diseases.

Initially, SPMs were obtained by extraction of animal tissue and further purification. But in the last two decades several synthetic strategies have been suggested to prepare SPM and related compounds.

When synthesized correctly, a sphingomyelin is a single molecular species composed of only one sphingoid base of a D-erythro configuration and one acyl chain (e.g. D-erythro N-palmitoyl sphingomyelin). Such SPMs are mainly obtained from milk or egg yolk and are present therein at very low concentrations. As a result, the extract it typically contaminated with other lipids, such as 1-alkyl-sn-glycerophoshoethanol amine and 1 alkyl-sn-glycerol phosphocholine [Do, U.H. and Ramochardarn, S. (1980) J. Lipid Res. 21, 888–894].

In addition, the extract may contain lipid contaminants which are resistant to known purification procedures. For example, milk derived lipids include a mixture of SPMs such as neutral glycosphingolipids and gangliosides [Martin, M.J., Martin-Sosa, S., Garcia-Pardo, L.A. and Hueso, P. (2001); J. Dairy Sci. 84, 995–1000; Martin, M.J., Martin-Josa, S. and Hueso, P. (2001) Lipids 36, 291–298], being resistant to alkaline hydrolysis and thus glycosphingolipids may contaminate milk-derived sphingomyelin. As appreciated by those versed n the art, glycosphingolipids, like peptides and proteins, may be immunogenic and thus their present in the extract is not preferable.

There are also reports that lipids derived of milk (including milk derived sphingomyelin) may be contaminated with bacterial products such as from Streptococcus agalacial [Bendle, P. and Vuyletelova, M. (1997) Vet. Med. 42, 71–80].

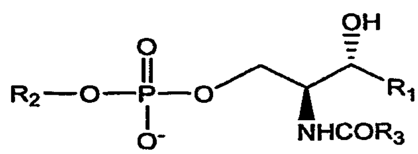
In addition, milk-derive SPM and egg-derived SPM are known to include mixtures of SPMs which vary in their acyl chains [see for example Avanti Polar Lipids Inc. Products Catalog Edition VI, p. 58]. Typically, milk-derived SPMs are enriched with C24:0 > C18:1 > C16:0 >> C18:0 and contain many other acyl chains. The very high percentage of these long acyl chais and therefore large mismatch between the two hydrocarbon chains makes this SPM very different from the egg-derived SPMs. The level of chain mismatch is a very important parameter in determining the physicochemical properties of SPMs [rev. in

Barenholz, Y. and Thompson, T.E. (1999) Chem. Phys. Lipids 102, 29–34; Barenholz, Y. and Thompson, T.E. (1980) Biochim. Biophys. Acta 604, 129–158; Barenholz et al. (1976) Biochemistry 15, 2441–2447]. A major difference in the ability of the two SPMs to suppress intestinal cholesterol absorption by decreasing thermodynamic activity of cholesterol monomers was recently observed [Eckhardt, E.R., Wang, D.Q., Donovan, J.M. and Carey, M.C. (2002) *Gastroenterology* **122**, 948–956]. In addition, the SPMs derived of natural sources have more than one sphingoid base. Although C18 D-erythro sphingosine is the main sphingoid base, other sphingoid bases accompany the main base in significant percentage. Especially the sphingoid base dihydrosphingosine (which is saturated and lacks the *trans* double bond between C4–C5), and smaller amounts of sphingosine and dihyrosphingosine bases other than C18 [Morrison, W.R. (1973) *Biochim. Biophys. Acta* **316**, 98–107; Morrison, W.R. and Hay, J.D. (1970) *Biochim. Biophys. Acta* **202**, 460–467; Morrison, W.R. (1969) *Biochim. Biophys. Acta* **176**, 530–539]. Both egg yolk derived SPM and milk-derived SPM sphingoid base and acyl chain composition is affected by diet and therefore batch to batch variation in sphingoid and acyl chain composition may occur and should be carefully studied. Such changes may also be reflected in the physicochemical and biological properties of the different batches.

DESCRIPTION OF THE INVENTION

In the following description reference numbers are used in brackets to denote a specific general formula. For example, in the following description sphingomyelin (1) denotes a sphingomyelin of the general formula (1) as defined hereinbelow.

Numerous attempts have been made to develop synthetic routes for the production of sphingomyelin (1) and its analogs:



Formula 1

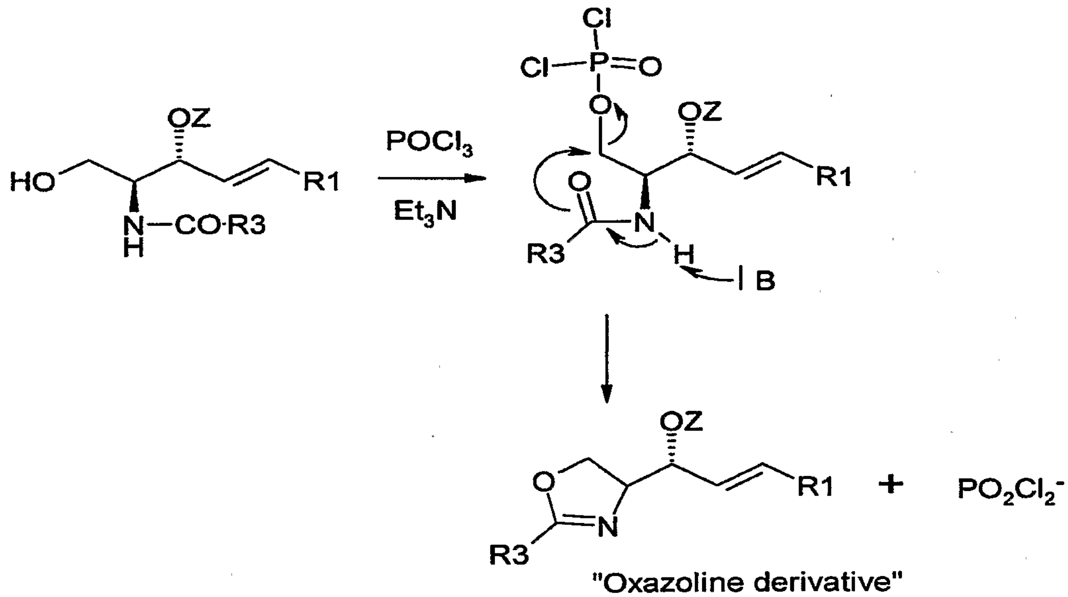
R_1, R_2 and R_3 being aliphatic or aromatic carbohydrate groups, such as an alkyl, alkenyl, alkynyl, cycloalkyl, aryl etc.

Currently SPMs may be obtained from natural sources or synthetically in small scale production. The synthetic approaches exerted by different groups vary mainly by the strategy of introducing the phosphate moiety into the ceramide backbone. Most of the procedures are multistep procedures, which require isolation and purification of the intermediates (typically by column chromatography). The procedures described in the art use appropriately substituted phosphoryl chlorides [Shapiro and Flowers, 1961; Dong, Butcher and Jared, 1991] or phosphoramidites [Bruzik, 1986, 1988; Kratzer and Schmidt, 1993; Bittman et al., 1991, 1994] as phosphorylation reagents.

One procedure described by Bruzik et al. [Bruzik 1988, ibid.] exhibits a one-pot procedure, however, the reagents employed, phosphoramidites, are rather expensive, extremely sensitive to the reaction and storage conditions and hence are considered inconvenient for scaling up of SPM production.

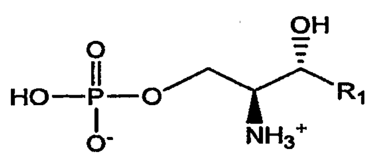
The present invention is based on the surprising finding that an inexpensive and widely available reagent $POCl_3$, which is extensively utilized for several decades in phospholipids synthesis [Eibl et al. 1970, 1978, 1987], is suitable for the production of sphingolipids.

Hitherto, the use $POCl_3$ for phosphorylation of suitably 3-O-protected ceramides resulted in intramolecular substitution of the highly nucleofugal (active leaving group) $-OPOCl_2$ group by the neighboring NHCO carbonyl, resulting in the formation of the corresponding oxazoline derivative. This undesired reaction is depicted in the following Scheme 1:



Scheme 1

It has now been found that sphingomyelin (**1**), sphingosine-1-phosphate (**5**) and their stereoisomer as well as their chemical analogs may be prepared by an economically feasible procedure, making use of widely available phosphorylation reagents. The general formula of sphingosine-1-phosphate (**5**) according to the invention is:



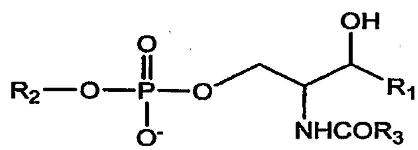
Formula 5

wherein R_1 is as defined for the sphingomyelin (**1**). The procedure according to the invention preferably utilizes as starting material 3-O- and N-protected sphingoid bases.

Currently available procedures which make use of 3-O- and N-protected sphingoid bases involve three protection-deprotection steps accompanied by the

isolation and purification of the intermediates obtained. A one-pot procedure has now been developed and is disclosed herein.

Thus, the present invention provides by a first of its aspects a sphingomyelin of the general formula (**1a**):



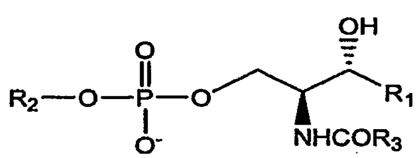
Formula (1a)

wherein

R_1, R_2 and R_3, which may be the same or different, represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl groups and said cycloalkyl aryl or heteroaryl groups may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl groups or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group;

provided that when said R_3 represents a palmitoyl group, R_1 cannot represent trans-$CH{=}CHC_{13}H_{27}$ and R_2 cannot represent $CH_2CH_2N^+(CH_3)_3$.

A preferred embodiment of the invention concerns the 2S, 3R steroisomer of said compound and having the following formula (**1**)



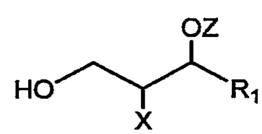
Formula (1)

wherein R_1, R_2 and R_3 are as defined.

The sphingomyelin according to the invention may have numerous applications. As indicated hereinbefore, sphingomyelins are excellent candidates for drug delivery formulations based on liposomes and other lipid assemblies as well as inducing reverse cholesterol transport in cardiovascular diseases. The person skilled in the art will recognize the pharmacological and biochemical potential of the sphingomyelins according to the invention and how they can be used in the medicinal industry.

The invention also provides a process for the preparation of a sphingomyelin of formula **(1a)** or **(1)**. According to the invention the process comprises the steps of:

(a) reacting with a phosphorylating reagent a 3-O-protected sphingoid compound of the following formula **(2a)**:



Formula (2a)

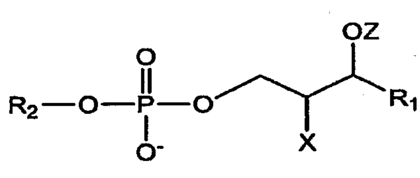
wherein

Z represents a protecting group;

X represents an amine or an amino precursor; and

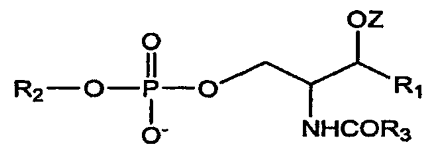
R_1 is as defined above;

(b) adding to the reaction mixture an alcohol of the formula R_2OH, in the presence of an aqueous base or aqueous acid to obtain a R_2-substituted phosphosphingoid of the formula **(7a)**;



Formula (7a)

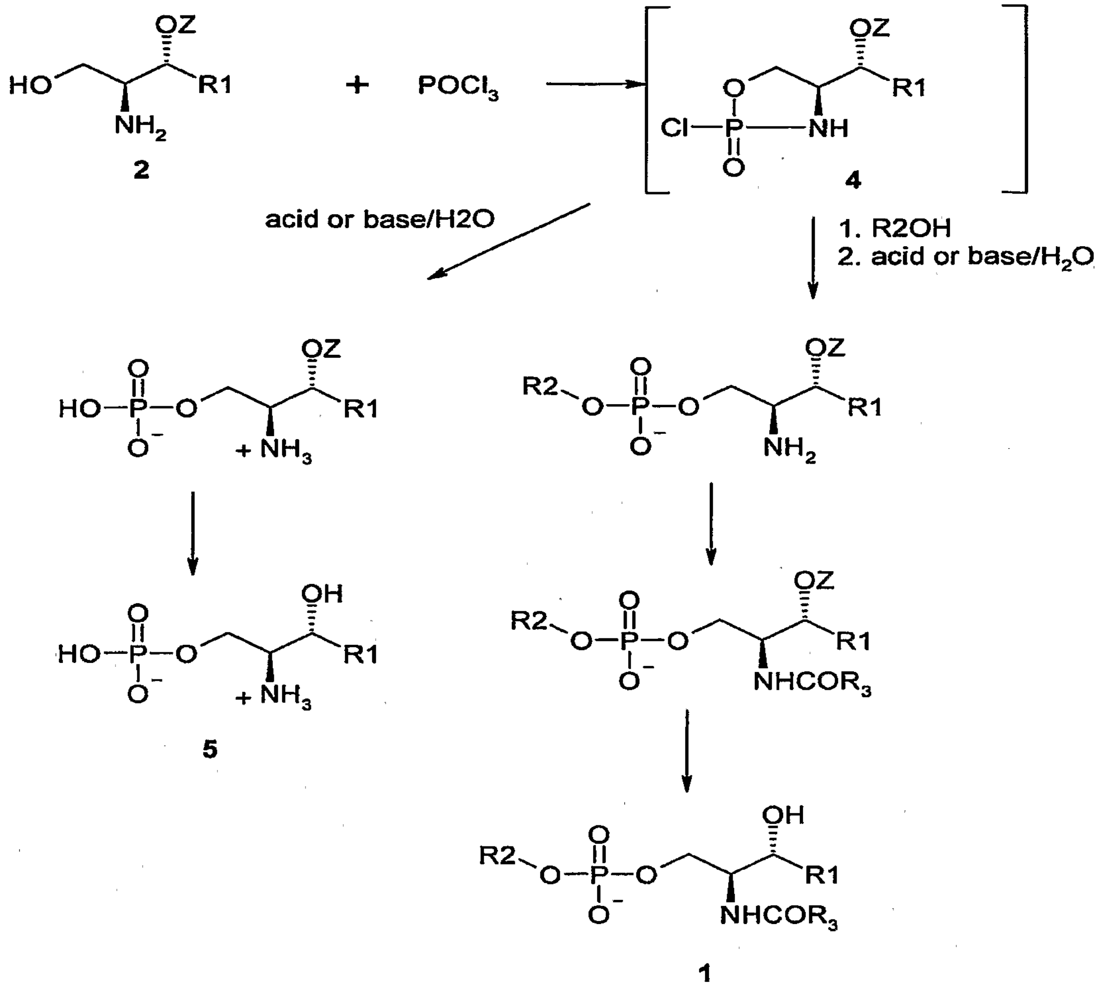
(c) mixing said R_2-substituted phosphosphingoid of the formula (**7a**) with an R_3 substituted amino acylating agent to obtain a phosphosphingoid of formula (**8a**):



Formula (8a)

(d) removing from said phosphosphingoid of formula (**8**) the 3-O-protecting group, Z, to obtain said sphingomyelin of formula (**1a**).

The process of the invention is schematically illustrated in the following, non-limiting , Scheme 2 (with respect to the 2S, 3R steroisomer), in which X is an amine.

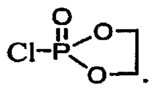


Scheme 2

The process of the invention may also comprise one or more purification steps. According to a preferred embodiment the final product may be purified by initial filtration followed by column chromatography on Silica gel using CH_2Cl_2.

According to the invention preferred Z protecting groups are, without being limited thereto, methoxymethyl (MOM), tetrahydropyranyl (THP), diphenylmethyl, triethylsilyl (TES), *t*-butyldimethylsilyl (TBDMS), mesitoate, 9-fluorenylmethyl carbonate (f-moc) , t-butyl carbamate (t-boc).

Preferred phosphorylating reagents are, without being limited thereto, $POCl_3$, ethylene chlorophosphite, methyl phosphodichloridite, chloro-N,N-diisopropylaminomethoxyphosphite, $[(isopropyl)_2N]_2POCH_2CH_2CN$, or

.

Preferred alcohols of the formula R_2OH are, without being limited thereto, choline, N-protected ethanolamines, oligoethyleneglycol monoethers, polyethyleneglycol monoehthers, polyethers, or suger derivatives.

The aqueous base according to the invention may be any organic or inorganic base known in the art of organic synthesis. Non-limiting examples of such aqueous bases include tri-, tetra- ethylamine, sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide or any alkali metal or alkali earth metal, known to be used as bases in organic reactions.

The aqueous acid according to the invention may be any organic or inorganic acid known in the art of organic synthesis. Preferred acids are Lewis acids. According to one embodiment, the Lewis acid is tetrabutyl ammonium fluoride.

According to one embodiment, the R_3 substituted amino acylating agent has the formula W-C(O)-R_3, wherein W is a leaving group. Preferred W are selected from Br, Cl, and R_3-(O)C-, more preferably, the amino acylating agent is Cl-C(O)-R_3, with R_3 as defined above.

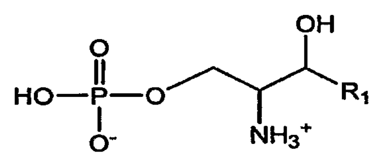
Preferred X groups, being defined as either an amino or a precursor of an amino groups are, without being limited thereto, amine, azido, hydrazine, -N=NH, or any other suitable N-containing group, known in the art of organic synthesis.

According to a preferred embodiment, the process of the invention may be performed as a single pot process.

According to yet another preferred embodiment, the process of the invention enables the large scale production of sphingomyelins of the formula **(1a)** and more preferably of the formula **(1)**.

Evidently, any sphingomyelin produced by the process of the invention as defined above, forms part of the present invention.

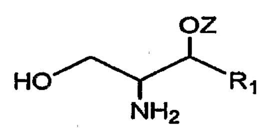
The invention also provides a process for the production of a phosphosphingoid of formula **(5a)**:



Formula (5a)

wherein R_1 is as defined above. The process comprises the steps of:

(a) reacting a 3-O-protected sphingoid of the following formula **(2a)**:



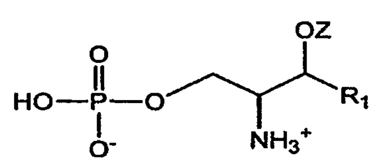
Formula (2a)

wherein

Z is as defined above;

with a phosphorylating reagent;

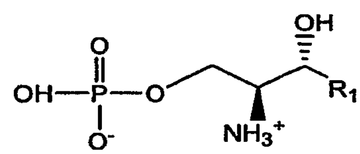
(b) adding to the reaction mixture an aqueous base or aqueous acid to obtain a phosphosphingoid compound of the formula **(9a)**;



Formula (9a)

(c) removing from said phosphosphingoid compound of the formula **(9a)** the 3-O-protecting group so as to obtain said phosphosphingoid of formula **(5a)**.

According to one preferred embodiment, the phosphosphingoid compound of formula **(5a)** is a 2S, 3R steroisomer of said compound having the following general formula **(5)**

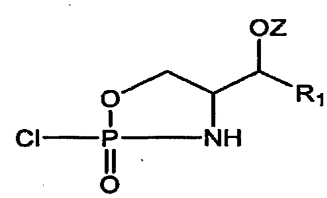


Formula (5)

wherein R_1 is as defined.

Evidently, any phosphosphingoid of formula **(5a)** or **(5)**, whenever prepared by the above defined process, forms part of the invention.

The invention also provides an oxazaphospholane compound of the following formula **(4a)**:

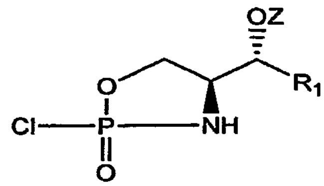


Formula (4a)

wherein

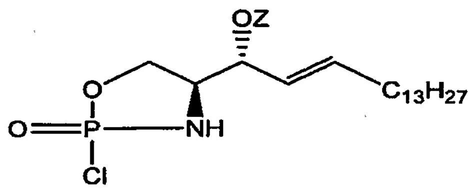
R_1 and Z are as defined above.

According to a preferred embodiment, the oxazaphospholane compound of formula **(4a)** is the 2S, 3R steroisomer of said compound and has the following formula **(4)**:

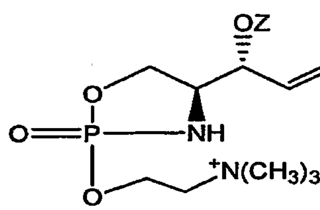


Formula (4).

Specific examples for oxazaphospholane compound according to the invention include those of the following formulae (4` and 4``):

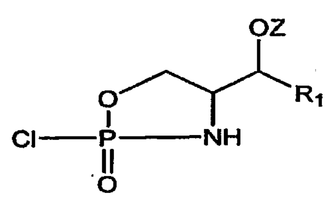


Formula 4`



Formula 4``

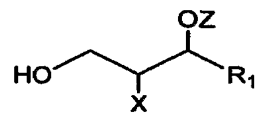
The invention also provides a process for the production of an oxazaphospholane compound of the following formula (**4a**):



Formula (4a)

wherein R_1 and Z are as defined above. The process comprises:

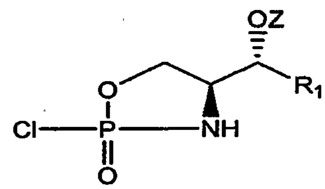
(a) reacting with a phosphorylating reagent a 3-O-protected sphingoid compound of the following formula (**2a**):



Formula (2a)

wherein X is an amine or an amino precursor.

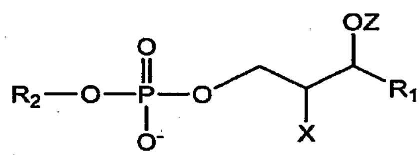
According to a preferred embodiment, the oxazaphospholane compound is a 2S, 3R steroisomer having the following general formula (4):



Formula (4).

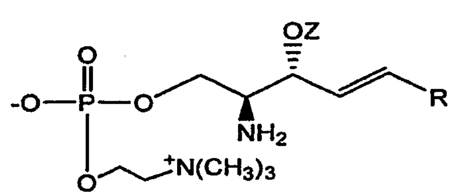
Evidently, any oxazaphospholane of the formula **(4a)** or of formula **(4)**, as defined and whenever prepared by the process of the invention also forms part of the invention.

The invention also provides an acyclic oxazaphospholane compound having the following formula **(7a)**:



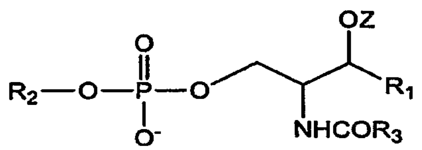
Formula (7a)

wherein R_1 and R_2, which may be the same or different, and Z and X are as defined above. A preferred compound of formula **(7a)** has the following structure (wherein R is as defined for R_1):



Formula 7`

Yet further, the invention provides an acyclic oxazaphospholane compound having the following formula (**8a**):

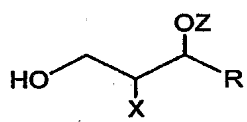


Formula (8a)

wherein

R_1, R_2 and R_3, which may be the same or different, and Z are all as defined above.

Finally, the invention provides a process for the production of a protected sphingoid of the following general formula (**2a**):

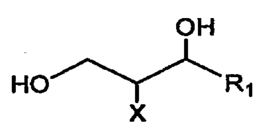


Formula 2a

wherein R is as defined for R_1, R_2 or R_3 above, X and Z is also as defined above.

The process comprises the steps of:

(a) reacting the diolamine compound of the following formula (**3a**):



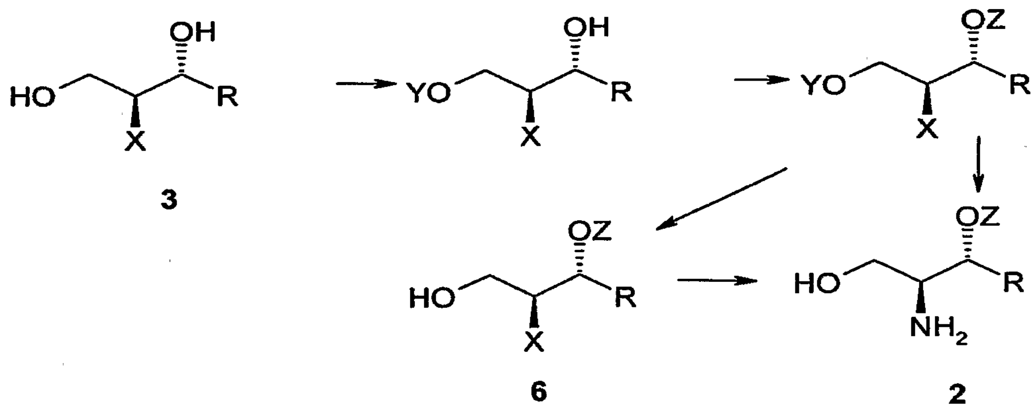
Formula 3a

with a selective primary alcohol protecting group;

(b) protecting the secondary amine with a protecting group;

(c) removing the protecting group from said primary alcohol.

The process of preparing said protected sphingoid of the following general formula (**2a**) is illustrated in the following Scheme 3:



Scheme 3

The invention will now be described by way of examples. While the foregoing description describes in detail only one specific embodiment of the invention, it will be understood by those skilled in the art that the invention is not limited thereto and that other sphingoid and phosphosphingoid compounds may be obtained, without departing from the scope of the invention as defined herein.

SPECIFIC EXAMPLES

Synthesis of 3-O-*tert* Butyldiphenylsilyl-D-erythro-sphingosine (2)

N-tert-Butoxycarbamoyl-D-erythro-sphingosine (**3**) (670 g, 1.67 mol) was dissolved in dry dichloromethane (12 L) and imidazole (284 g, 4.18 mol) and *tert*-Butyldimethylchlorosilane (277 g, 1.84 mol) were subsequently added. After stirring for 2.5 h at room temperature (RT) the reaction was completed and additional amounts of imidazole (114 g, 0.75 mol) and *tert*-Butyldiphenylchlorosilane (686 ml, 2.2 mol) were added. The reaction mixture

was stirred for an additional period of 12 h followed by washing with water, evaporated and redissolved in EtOH (18 L).

To the redisolved solution concentrated aqueous HCl (4 L) was added slowly and the solution was stirred at 40°C for 2 h. The solution was then cooled to 0°C and cold solution of NH_4OH (3.5 L, 26%) was added slowly for neutralization. The mixture was filtered, dried, evaporated and the residue was purified on Silica gel column, using the gradient $CHCl_3$: MeOH 95.5:0.5 to 97:3 as eluent.

Yield of 500 g (56 % from the initial N-Boc-Sphingosine) of (**2a**) as yellowish oil was obtained.

^{1}H NMR 300 MHz (δ ppm, $CDCl_3$) : 0.88 (t, 3H), 1.06 (s, 9H), 1.15 (bm, 4H), 1.26 (bs, 18H), 1.81 (bm, 5H), 2.80 (m, 1H), 3.435 (m, 1H), 3.61 (m, 1H), 4.015 (m, 1H), 5.28 (m, 2H), 7.37 (m, 6H), 7.65 (m, 4H)

Synthesis of (4S)-4- [(1R)-1-(*tert*-Butyldiphenylsilyloxy)-hexadec-2-enyl]-2-chloro-2-oxo-[1,3,2]-oxazaphospholidine (4)

To a solution of freshly distilled $POCl_3$ (13 ml, 21.7 g, 142 mmol) in hexane (100 ml) a solution of dry triethylamine (40 ml, 29.1 g, 288 mmol) in dichloromethane (60 ml) was added at -10°C with stirring and under a dry nitrogen atmosphere. The solution thus obtained was cooled to -20°C and a pre-cooled solution of **2** (50 g, 93 mmol) in dichloromethane (500 ml) was added. The solution of compound (**4**) thus obtained was used as such for preparation of phospholipids of formula (**1**).

Synthesis of 1-O-Phosphocholino- (2S, 3R)-2-hexadecylamido-octadec-4-ene-1, 3-diol (1) (N-palmitoyl-sphingosyl phosphocholine, N-palmitoyl sphingomyelin)

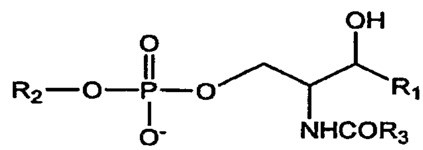
To the solution comprising compound **4** a solution of choline tosylate salt (86 g, 312 mmol) in dry MeCN (1.5 L) was added followed by a solution of triethylamine (20 ml) in dichloromethane (30 ml) and the mixture was stirred at

RT for 12 h. The reaction mixture was then concentrated, co-evaporated three times with hexane, redissolved in THF (2.5 L), filtered and hydrolyzed with 11 ml of concentrated aqueous HCl. Then the solution was dried with $MgSO_4$ and reacted with palmitoyl chloride (31 ml, 28 g, 102 mmol) in the presence of excess of triethylamine. The solution was filtered, evaporated, redissolved in dichloromethane, washed several times with $MeOH/H_2O$, dried, evaporated and the residue was reacted with excess of tetrabutylammonium fluoride 1M solution in THF at 45°C.

After completion the solution was evaporated, the residue re-dissolved in dichloromethane, washed with $MeOH/H_2O$, concentrated and precipitated in acetone. The crude sphingomyelin thus obtained was filtered and purified by column chromatography on Silica gel using CH_2Cl_2:MeOH:H_2O 65:25:4 as eluent to yield 20 g (31% from **2**) of **1** as white solid. ^1H NMR 300 MHz (δ ppm, CD_3OD) : 0.89 (t, 6H), 1.28 (bm, 44H), 1.37 (bm, 2H), 1.56 (bm, 2H), 2.015 (m, 2H), 2.17 (m, 2H), 3.21 (s, 9H), 3.62 (m, 2H), 3.90-4.12 (m, 4H), 4.26 (m, 2H), 5.435 (dd, 1H), 5.69 (dt, 1H)

CLAIMS:

1. A sphingomyelin of the general formula (**1a**):



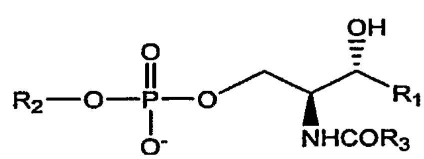
Formula (1a)

wherein

R_1, R_2 and R_3, which may be the same or different, represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl groups and said cycloalkyl aryl or heteroaryl groups may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl groups or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group;

provided that when said R_3 represents a palmitoyl group, R_1 cannot represent trans-$CH{=}CHC_{13}H_{27}$ and R_2 cannot represent $CH_2CH_2N^+(CH_3)_3$.

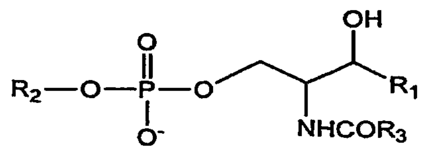
2. The compound of Claim 1, being an 2S, 3R steroisomer of said compound and having the following formula (**1**)



Formula (1)

wherein R_1, R_2 and R_3 are as defined.

3. A process for the preparation of a compound of the following formula (**1a**):



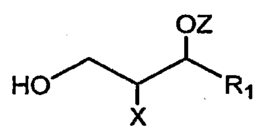
Formula (1a)

wherein

R_1, R_2 and R_3, which may be the same or different, represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl groups and said cycloalkyl or aryl groups may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl groups or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group;

the process comprises the steps of:

(a) reacting with a phosphorylating reagent a 3-O-protected sphingoid compound of the following formula **(2a)**:



Formula (2a)

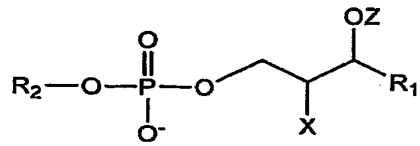
wherein

Z represents a protecting group;

X represents an amine or an amino precursor; and

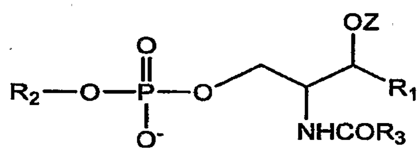
R_1 is as defined above;

(b) adding to the reaction mixture an alcohol of the formula R_2OH, in the presence of an aqueous base or aqueous acid to obtain a R_2-substituted phosphosphingoid of the formula **(7a)**;



Formula (7a)

(c) mixing said R_2-substituted phosphosphingoid of the formula **(7a)** with an R_3 substituted amino acylating agent to obtain a phosphosphingoid of formula **(8a)**:

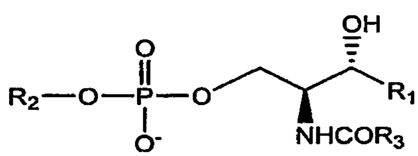


Formula (8a)

(d) removing from said phosphosphingoid of formula **(8)** the 3-O-protecting group, Z, to obtain said sphingomyelin of formula **(1a)**.

4. The process of Claim 3, comprising a purification step of said sphingomyelin of formula **(1a)**.

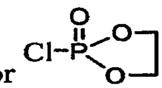
5. The process of Claim 3 or 4, wherein said sphingomyelin is a 2S, 3R steroisomer of said compound having the following general formula **(1)**



Formula (1)

wherein R_1, R_2 and R_3 are as defined.

6. The process of Claim 5, wherein said Z is a protecting group selected from methoxymethyl (MOM), tetrahydropyranyl (THP), diphenylmethyl, triethylsilyl (TES), *t*-butyldimethylsilyl (TBDMS), mesitoate, 9-fluorenylmethyl carbonate (f-moc) , t-butyl carbamate (t-boc).

7. The process of any one of Claims 3 to 6, wherein said phosphorylating reagent is selected from $POCl_3$, ethylene chlorophosphite, methyl phosphodichloridite, chloro-N,N-diisopropylaminomethoxyphosphite, $[(isopropyl)_2N]_2POCH_2CH_2CN$, or .

8. The process of any one of Claims 3 to 7, wherein said R_2OH is selected from choline, N-protected ethanolamine, oligoethyleneglycol monoether, polyethyleneglycol monoehther, a polyether, or a suger derivative.

9. The process of any one of Claims 3 to 8, wherein said aqueous base is an organic or inorganic base.

10. The process of any one of Claims 4 to 8, wherein said aqueous acid is an organic or inorganic acid.

11. The process of Claim 10, wherein said acid is a Lewis acid.

12. The process of any one of Claims 3 to 11, wherein said R_3 substituted amino acylating agent has the formula W-C(O)-R_3, wherein W is a leaving group.

13. The process of Claim 12, wherein said W is selected from Br, Cl, and R_3-(O)C-.

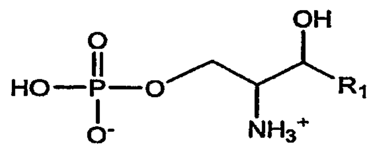
14. The process of Claim 13, wherein said R_3 substituted amino acylating agent is Cl-C(O)-R_3.

15. The process of any one of Claims 3 to 14, being a single pot process.

16. The process of any one of Claims 3 to 15, for large scale production of said sphingomyelin of formula **(1a)**.

17. A sphingomyelin of formula **(1)** or **(1a)** as defined in Claim 1 or 2, whenever prepared by the process of any one of Claims 3 to 16.

18. A process for the production of a phosphosphingoid of formula **(5a)**:



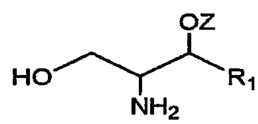
Formula (5a)

wherein

R_1 represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl groups and said cycloalkyl or aryl groups may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl groups or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group;

the process comprises the steps of:

(a) reacting a 3-O-protected sphingoid of the following formula (**2a**):



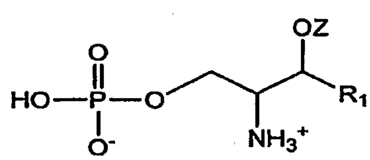
Formula (2a)

wherein

Z represents a protecting group; and R_1 is as defined above;

with a phosphorylating reagent;

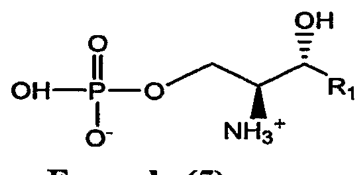
(b) adding to the reaction mixture an aqueous base or aqueous acid to obtain a phosphosphingoid compound of the formula (**9a**);



Formula (9a)

(c) removing from said phosphosphingoid compound of the formula (**9a**) the 3-O-protecting group so as to obtain said phosphosphingoid of formula (**5a**).

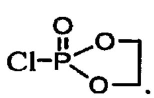
19. The process of Claim 18, wherein said phosphosphingoid compound is a 2S, 3R steroisomer of said compound having the following general formula (**5**)



Formula (5)

wherein R_1 is as defined.

20. The process of Claim 18, wherein said Z is a protecting group selected from methoxymethyl (MOM), tetrahydropyranyl (THP), diphenylmethyl, triethylsilyl (TES), *t*-butyldimethylsilyl (TBDMS), mesitoate, 9-fluorenylmethyl carbonate (f-moc) , t-butyl carbamate (t-boc).xxx

21. The process of Claims 18 or 19, wherein said phosphorylating reagent is selected from $POCl_3$, ethylene chlorophosphite, methyl phosphodichloridite, chloro-N,N-diisopropylaminomethoxyphosphite, $[(isopropyl)_2N]_2POCH_2CH_2CN$, or .

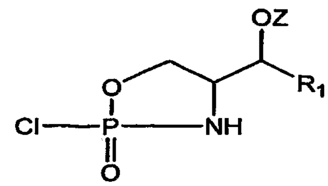
22. The process of any one of Claims 17 to 21, wherein said aqueous base is an organic or inorganic base.

23. The process of any one of Claims 18 to 21, wherein said aqueous acid is an organic or inorganic acid.

24. The process of Claim 18, wherein said acid is a Lewis acid.

25. A phosphosphingoid of formula (**5a**) or (**5**), whenever prepared by the process of any one of Claims 18 to 24.

26. An oxazaphospholane compound of the following formula (**4a**):



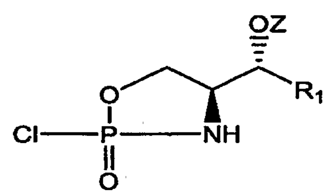
Formula (4a)

wherein

R_1 represents a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl group and said cycloalkyl or aryl may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group; and

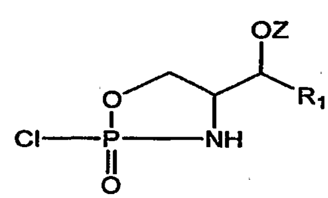
Z represents a protecting group.

27. The oxazaphospholane compound of Claim 26, being an 2S, 3R steroisomer of said compound and having the following formula (**4**):



Formula (4).

28. A process for the production of a oxazaphospholane compound of the following formula (**4a**):



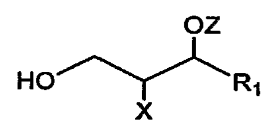
Formula (4a)

wherein

R_1 represents a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl group and said cycloalkyl or aryl may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group; and

Z represents a protecting group;

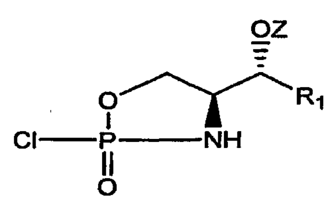
the process comprises reacting with a phosphorylating reagent a 3-O-protected sphingoid compound of the following formula (**2a**):



Formula (2a)

wherein R_1 and Z are as defined and X is an amine or an amino precursor.

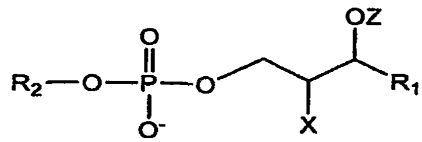
29. The process of Claim 28, wherein said oxazaphospholane compound is a 2S, 3R steroisomer having the following general formula (**4**):



Formula (4).

30. An oxazaphospholane of the formula (**4a**) or of formula (**4**), as defined in Claim 26 or 27, whenever prepared by the method of Claim 28.

31. An acyclic oxazaphospholane compound having the following formula (**7a**):



Formula (7a)

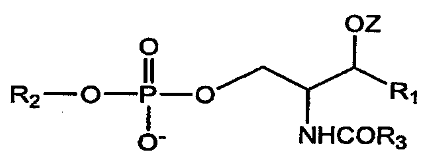
wherein

R_1 and R_2, which may be the same or different, represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl group and said cycloalkyl or aryl may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group; and

Z represents a protecting group; and

X represents an amino group or an amino precursor group.

32. An acyclic oxazaphospholane compound having the following formula **(8a)**:



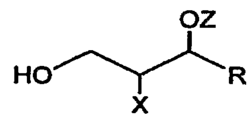
Formula (8a)

wherein

R_1, R_2 and R_3, which may be the same or different, represent a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl group and said cycloalkyl or aryl may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group; and

Z represents a protecting group.

33. A process for the production of a protected sphingoid of the following general formula **(2a)**:



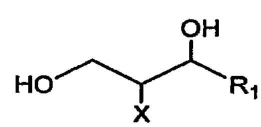
Formula 2a

wherein

- R represents a group selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, said alkyl, alkenyl or alkynyl may be straight or branched chains and may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, cycloalkyl or aryl group and said cycloalkyl or aryl may be substituted by one or more halide, amino, hydroxyl, nitro, sulfo, alkyl, alkenyl, alkynyl or by an alkylene-, alkenylene-, alkynylene-cycloalkyl or –aryl group;
- Z represents a protecting group;
- X represents an amino group of a precursor of an amino group;

the process comprises the steps of:

(a) reacting the diolamine compound of the following formula **(3a)**:



Formula 3a

(a) with a selective primary alcohol protecting group;

(b) protecting the secondary amine with a protecting group;

(c) removing the protecting group from said primary alcohol.